Estimating the separate effects of total and regional adiposity on plasma lipoproteins, an example where classical statistics do not apply

Short title: Estimating separate effects under nonclassical regression

Keywords: Regression, independence, triglycerides, body mass index, low-density lipoproteins, adiposity, lipoproteins

Abstract

Multiple regression analysis is used widely in epidemiological research to assess the separate effects of independent variables. The classical regression model assumes the relationships between variables are the same for different percentiles of the dependent variable. This assumption does not apply when relating adiposity to lipoproteins, i.e., the slopes relating the lipoproteins to adiposity increase in magnitude from the smallest to largest percentile of the HDL-cholesterol and triglyceride distributions. Therefore, the standard estimates of the separate effects of two or more adiposity measurements on lipoproteins the cannot be used because: 1) the results depend upon the specific level of adiposity the variables are adjusted to; and 2) the results are represented by a set of regression slopes rather than a single adjusted coefficient. A procedure is proposed for estimating the separate effects of two or more independent variables when the regression slope depends upon the percentile of the dependent variable. Our experience from these and other data suggest that classical model (parallel regression curves for different percentiles of the dependent variable) represent the exception rather than the rule, leading us to question whether multiple regression coefficients, pervasive in epidemiologic research, are reflective of the independent effects they purport to represent.

Higher adiposity levels are associated with higher plasma triglyceride and lower plasma concentrations of high-density lipoprotein (HDL)-cholesterol {1-12}. Waist circumference, a measure of visceral, male-type, or upper body fat, exhibits these associations whereas hip circumference, a measure of female-type adiposity, exhibits weaker associations with these lipoproteins and may even show the opposite effects {1,2}. Most studies that measured both total and regional adiposity include analyses of the independent effects of total and regional adiposity on plasma lipoproteins {5,8,9,11,12} using multiple regression analyses or partial correlation coefficients {5,8,9,11,12}.

In its simplest form, the classical regression model is:

$$y=\alpha+\beta x$$

where Y is the lipoprotein level, X is adiposity, "•" is the estimated change in Y (slope) per unit increase in X (simple linear model), and "•" is the intercept term. The intercept may not be of particular interest and is frequently not reported. The slope (β) describes the deterministic relationship between Y and X. The actual data points will not lie on the regression line but rather will be distributed above and below the line, presumably at random in accordance a probably density function ($f(\varepsilon)$) (Figure 1). Because $f(\varepsilon)$ does not depend upon X, the lines (or curves) designating the 2%, 16%, 84%, 98% or other percentiles for the distribution of points about the line are parallel to the regression line. The expected value for the kth percentile of Y (i.e., $y_{[k]}$) will given by the formula:

$$y_{[k]}= F^{-1}(k)+\alpha+\beta x$$

where $F^{-1}(k)$ is the inverse of the cumulative distribution of the residuals $f(\varepsilon)$. The probability density function $f(\varepsilon)$ of the residuals (ε) is usually assumed to be an appropriately scaled normal distribution. Thus classical model requires that the same regression slope (β) applies to all percentiles of the dependent variable, which corresponds to a series of parallel lines (or curves depending upon the complexity of the model) as depicted in Figure 1.

Elsewhere, it has been shown that the classical regression model does not apply when relating adiposity to HDL-cholesterol or triglyceride concentrations {13.14}. Specifically, this prior analyses suggests adiposity and lipoproteins are related by models of the form:

$$y_{[k]}= \alpha(k)+ \beta(k)x$$

where $\alpha(k)$ and $\beta(k)$ are functions of the kth percentile of the distribution of Y. At different percentiles k, the variables X and Y are no longer related to each other along parallel curves. For example, we have found that compared to the 5th percentile of the triglyceride distribution, the rise in men's triglycerides at the 95th percentile per unit of adiposity was fourteen-fold greater for BMI, 7.8-fold greater for waist circumference, 3.6-fold greater for hip circumference, and 4.4-fold greater for chest circumference. The rise in women's triglyceride concentrations at the 95th percentile was eight-fold greater than at the 5th percentile for each kg/m^2 increase in BMI{13}.

This paper examines the problem of assessing the separate effects of total and regional adiposity on plasma triglycerides and HDL-cholesterol concentrations when the classical model does not apply. We employ a solution that follows the rationale for the classical model, however, the results depend upon both the specific covariate and the percentile of the dependent variable (i.e., a surface in three dimensions) in contrast to the point estimates produced under the classical model.

METHODS AND MATERIALS

The statistical analyses are based on the cumulative distributions within the deciles of BMI, waist circumference, hip circumference, and chest circumference. Within each decile, we estimated the 5th through the 95th percentiles of the lipoprotein distribution. Simple least-squares regression analysis was used to estimate the rate of change at each lipoprotein percentile across the ten deciles of fetness. We applied simple linear regression to the ten bivariate observations consisting of the average adiposity (independent variable) and the kth percentile of the triglyceride distribution (dependent variable) within each declile of fatness category to estimate the change in the kth percentile of triglycerides per unit of adiposity. Since the usual underlying statistical assumptions presumably do not apply for percentiles (particularly those representing the tails of the distribution), we calculated the standard errors and significance levels by bootstrap resampling {15}. Bootstrap estimates were created as follows: 1) we sampled with replacement to create a bootstrap data set of adiposity and triglycerides; 2) we divided adiposity into deciles; 3) we then determined average adiposity and the percentiles of the triglyceride distribution within each decile; 4) across the ten deciles of fatness, we applied least squares regression to estimate at each percentile the apparent change in triglycerides per unit of adiposity; 5) we repeated steps 1-4 ten thousand times in order to obtain a sample of 10,000 regression slopes which were then averaged to produce the bootstrap estimate of the regression slopes. The standard deviations of these 10,000 regression slope provides the bootstrap estimate of the standard error of the regression slope. Two-tailed significance levels were calculated as 2*minimum (p, 1-p), in which p is the proportion of times that the bootstrap slopes were less than zero.

Adjusted regression slopes Multiple linear regression is the standard test for determining whether the independent effects of two independent variables on the dependent variable are significant. For example, in estimating the effects of waist circumference and BMI on plasma triglycerides, both waist circumference and BMI are included together as independent variables. Waist circumference would be concluded to have an independent effect on plasma triglycerides if its coefficient is significant in the model. The adjusted coefficient can be computed in stages {16}: 1) adjusting the independent variable (waist circumference) for the covariate (BMI) by simple linear regression; 2) adjusting the dependent variable (triglycerides) for BMI by simple linear regression; 3) estimating the regression slope for the adjusted triglycerides (dependent variable) versus adjusted waist circumferences (independent variable) by simple linear regression. The regression slope from step 3 represents the effect of waist circumference on triglycerides adjusted for BMI (this is identical to the coefficient for waist circumference in a multiple linear regression analyses that includes BMI as a second independent variable).

Stages one and two can be described as the projection of the points onto a vertical line by the family of curves that pass through the data points and are parallel to the fitted regression line. The upper panel of Figure 2 displays the adjustment of triglycerides for BMI in stage 2. The traditional regression model assumes that the slope between triglycerides and BMI is the same for all percentiles of the triglyceride distribution (Figure 2 upper panel), so that the particular choice of BMI that the triglyceride values are adjusted to does not affect the estimate of adjusted regression slope. Specifically, the dashed arrows show the adjustment to a BMI of 25 and the solid arrows show the adjustment to a BMI of 20. Different choices for BMI affect the adjustment by adding different constants to all of the adjusted values (the same constant to each point), but do not affect the relative positions of the adjusted values to each other (Figure 2, upper panel). Similarly, adjusting waist circumference to a BMI of 20, 30, or 400 will yield a set of adjusted waist circumferences that will have the same relative position to each other, and the only effect of the particular choice of BMI used in the adjustment will be a shift up or down for the entire set of waist circumferences. Thus adjusting triglycerides and waist circumference to a BMI of 20, 30 or 400 yields exactly the same adjusted coefficient for triglycerides versus waist circumferences (even if triglycerides and waist circumference are adjusted to different BMIs, the regression slope for adjusted triglycerides versus adjusted waist circumference will be the same).

The same three-step procedure was used to estimate the relationship between triglycerides and waist circumference adjusted for BMI when the relationship between triglycerides and BMI are not parallel (i.e., the slope for triglycerides versus BMI depends upon the percentile of the triglyceride distribution): 1) We adjusted triglyceride values by projecting each observed triglyceride value onto a vertical line (specified BMI) using the family of lines that pass through the data point and have the slope corresponding to the data point's percentile within the triglyceride distribution (Figure 2, bottom). 2) Using the same procedure we adjusted the waist circumferences by projecting each observed waist circumference to its expected value for the specified BMI based upon the slope for its percentile within its distribution. 3) We determined the regression slopes for the adjusted triglyceride versus adjusted waist circumferences for each percentile of the triglyceride distribution using the bootstrap procedure described above. Because the regression slopes are not parallel, the relationship between the points in step one and two will be different for different choices of BMI. Therefore, unlike the special case of parallel regression slopes in the classical regression model, the regression slope for adjusted triglycerides versus adjusted waist circumferences will depend upon the choice of BMI that the triglyceride and waist circumference values are adjusted to. Results are presented for adjustment at a BMI selected near its median and above and below the 95th and 5th percentile of the BMI distribution to assess the sensitivity of the adjustment to the particular choice of BMI.

RESULTS

The design and subject characteristics of this cohort are described in detail elsewhere {17,18}. Plasma triglycerides averaged (SD) 1.160 (0.717) mmol/L in men and 0.926 (0.603) mmol/L in women, and plasma HDL-cholesterol averaged 1.339 (0.351) and 1.650 (0.412) mmol in men and women. respectively. The men were generally lean as indicated by their BMI {23.776 (2.475) kg/m^2} and circumferences of the waist {0.849 (0.060) m}, hip {0.952 (0.071) m}, and chest {1.016 (0.069) m}. The women were also generally lean as indicated by their BMI {21.326 (2.482) kg/m2} and circumferences of their waist {0.686 (0.069) m}, hip {0.919 (0.065) m}, and chest {0.880 (0.053) m}. Table 1 shows that in men, BMI was most strongly correlated with waist circumference and more weakly correlated with hip circumference, whereas in women the correlation among the adiposity measurements were all of similar magnitude.

Standard regression analyses Table 2 presents the classical regression estimates of the effects of adiposity on plasma triglyceride and HDL-cholesterol concentrations. In both men and women, the unadjusted BMI and circumferences of the waist and chest were concordantly related to plasma triglycerides and inversely related to HDL-cholesterol concentrations. The regression slopes for triglycerides were nearly twice as large or larger in men than women. Men's and women's slopes for HDL-cholesterol were more similar to each other, except for chest circumference, which was larger in women.

Adjustment for BMI reduced the slopes relating men's waist circumferences to their triglycerides and HDL-cholesterol by at least two-thirds, although statistical significance was maintained. In women, adjustment for BMI had a somewhat smaller effect on these relationships. Adjustment for BMI eliminated the relationship between chest circumference and triglycerides in both sexes, and substantially reduced the relationship of chest circumference to HDL-cholesterol in men but not women. In women, Adjusting the regression slopes of triglycerides and HDL-cholesterol versus BMI for waist circumference had a larger effect in women than in men.

Men's hip circumferences were concordantly related to triglycerides and inversely related to HDL-cholesterol but not when adjusted for BMI or waist circumference. Adjustment for chest circumference diminishes by half the slopes for hip circumference versus triglycerides and HDL-cholesterol. In women, hip circumference is inversely related to triglycerides when adjusted for BMI but not without adjustment or when adjusted for BMI or chest circumference.

BMI versus regional adiposity Figure 3 plots the regression slopes for BMI (dependent variable) versus waist, hip, and chest circumference for different percentiles of the BMI distribution. For example, the regression slope for men's BMI versus waist circumference (kg/m^2 per meter) was 22.5 at the 10th percentile of the BMI distribution (i.e., the 10th percentile of the BMI distribution rose 22.5 kg/m^2 with each one meter increment in waist circumference). The regression slopes for men's BMI versus waist circumference was 23.56 at the 25th percentile, 25.5 at the 50th percentile, 30.76 at the 75th percentile, and 35.26 at the 90th percentile of the BMI distribution. Thus the increase in men’s BMI per meter of waist circumference increased more rapidly at the higher percentiles of the BMI distribution than at the lower percentiles (in contrast, under the classical regression model of Figure 1 the increase would be the same at all percentiles and the line would be flat). In men the slope for hip circumference versus BMI was relatively constant (flat line, suggest the classical model may apply), however the slopes for BMI versus chest circumference increases for higher BMI percentiles.

In women, the regression slopes for body circumferences (independent variables) versus BMI (dependent variable) are not the same at all BMI percentiles (i.e., the curves for the slopes are not flat lines when plotted against BMI percentiles), suggesting that classical statistical adjustment is inappropriate. All three circumferences measurements have regression slopes that increase from the 5th to the 95th BMI percentiles. For example, each meter increase in waist circumference was associated with a 13.0 kg/m^2 increase in the 5th BMI percentile, an 18.6 kg/m^2 increase at the 25th BMI percentile, a 22.6 kg/m^2 increase at the 50th percentile, a 26.0 kg/m^2 increase at the 75th percentile. 31.9 kg/m^2 increase at the 90th percentile, and 39.5 kg/m^2 increase at the 95th BMI percentile.

Plasma triglyceride concentrationss in men Figure 4 (upper panel) displays the plot of the regression slopes for BMI versus different percentiles of the plasma triglyceride distribution. Plots are presented without adjustment (solid curve) and when adjusted for circumferences of the waist, hip and chest (dashed curves). The adjusted curves were adjusted to the median for waist, hip and chest (adjustment to the 5th or 95th percentiles produced approximately the same results as adjustment to the median). The adjustments had little effect on the curve, suggesting that in these men waist, hip and chest circumference do not further explain the association between plasma triglycerides and adiposity. Both the adjusted and unadjusted slopes were significant for all percentiles between the 5th and the 95th percentile.

Figure 4 (middle panel) shows the effect of adjusting the relationship between waist circumference and plasma triglyceride concentrations (solid line) for BMI (dashed line). The unadjusted regression slopes show that the association becomes progressively greater from the 5th through the 95th triglyceride percentile. The slopes were made substantially smaller by adjustment for BMI, albeit still significant between the 7th and 91st triglyceride percentiles.

Figure 4 (bottom panel) presents the slopes for plasma triglycerides versus hip and chest circumferences in men, The dashed curves were adjusted for BMI and the solid curves were not. In both, the significance of the slopes are completely eliminated by adjustment for BMI. Without adjustment, hip circumferences were associated concordantly with increases in the 7th through the 95th percentiles of the triglyceride distribution, and chest circumferences were associated concordantly with increases in the 5th through the 95th triglyceride percentiles.

Plasma triglyceride concentrationss in women We have previously reported that the slopes relating women's plasma triglyceride concentrations to BMI increase linearly between the 5th and 84th percentile and then increases sharply {13}. Figure 5 (upper panel) shows that adjustment for waist eliminates the relationships of BMI to all triglyceride percentiles, whereas adjustment for chest has no effect. These adjustments yielded essentially the same results irrespective of whether we adjusted to narrow, intermediate, or large body circumferences. In contrast adjusting the BMI-triglyceride slopes for hip circumference depended in part upon the broadness of the hips ; i.e., whether the adjustment were made to broad, intermediate or narrow hips. Specifically, adjustment to a large hip circumference did not change the relationship (not displayed), whereas adjustment to the median hip circumference or narrowest hips increased the estimated effect of BMI on triglycerides (specifically triglycerides percentiles between the 50th and 90th).

We have also reported that women's unadjusted waistlines primarily impact the higher percentiles of their triglyceride distribution, whereas the impact of their unadjusted hips was the same throughout the triglyceride distribution{13}. We found that plasma triglycerides were more strongly affected by waist circumference after adjustment for hip circumferences and conversely, triglycerides are more strongly affected by hip circumferences after adjustment for waistlines. These are shown in the middle and bottom panels of Figure 5. Without adjustment, triglycerides were essentially unrelated to hip circumference. When adjusted for waist, there appeared an inverse relationship between hip circumference and plasma triglyceride percentiles at the 70th percentile and above.

HDL-cholesterol concentrations in men Figure 6 (upper panel) presents the plot of the regression slopes that relate HDL-cholesterol to BMI in men. The unadjusted curve shows that the slope becomes progressively more negative from the 5th to the 95th percentile, and that the progressive decrease of the slopes is linear. The curve remains linear when adjusted for waist circumference, however, it is shifted towards zero when adjusted, with the magnitude of the shift towards zero being greater when adjusted to a broader waistline than a small waist line. The plot of the regression slopes for HDL versus waist circumference is also increasing negative as the percentile of the HDL distribution is increased. The relationships are weakened when adjusted for BMI (particularly to intermediate and heavier BMI), albeit they remain significant for all percentiles.

The unadjusted regression slopes for HDL-cholesterol versus hip circumference appear to be the same for all percentiles of the HDL-cholesterol distribution (consistent with the classical model). The curve is flat and the regression coefficients are significantly less than zero for all HDL-percentiles between the 5th and 95th percentile. Adjusting the regression slopes for BMI moves the curve to coincide with the x-axis, showing that all of the adjusted regression slopes are essentially zero (similar results regardless of the particular choice of BMI).

DISCUSSION

The classical regression model assumes that the relationships of triglycerides and HDL-cholesterol to adiposity are the same throughout the lipoprotein distribution, (Figure 1) which we have shown to be untrue (Figures 4-6). The deviations from the classical model are sufficiently large as to lead us to conclude that the classical regression model, albeit convenient and tractable, may bear little relevance to the relationship of lipoproteins to adiposity. Other relationships we have found to deviate significantly from the classical model include the relationships adiposity to physical activity (the decrease in weight per km run being 3 fold greater at the 95th than 5th percentile {14}) and HDL-cholesterol to physical activity (two and fifty-fold differences at the 95th vis-a-vis 5th percentile in men and women respectively {14}) and alcohol (two and three fold differences in the effect per drink at the 5th vis-a-vis 95th percentiles in men and women, respectively {14}).

An example where the classical model applies An example from these data can be found where the classical model gives the right answer-the relationship of of plasma HDL-cholesterol levels to hip circumference (Figure 6, bottom panel). The unadjusted curve is essentially a flat horizontal line, suggesting that the same regression slope applies throughout the HDL-cholesterol distribution (estimated as -0.494 (0.082) by the classical model. The curve relating BMI (independent variable) to hip circumference (dependent variable) is also fairly flat (not presented), suggesting that the same slope applies throughout the range of hip circumferences. Adjusting for BMI repositions the curve proximal to the x-axis. None of the adjusted regression slopes are significant different from zero for any percentile of the HDL-cholesterol distribution. Most of the remaining examples revealed significant departures from the classical model.

An example where the classical model doesn't apply but gives the right result Table 2 shows that under the classical model, the significant regression slopes for men's triglycerides versus waist and triglycerides versus hip circumferences become nonsignificant when adjusted for BMI. The classical model does not apply because there is a significant increase in the regression slopes for triglycerides versus hip and triglycerides versus chest circumference as the percentile of the triglyceride distribution increase from the 5th to the 95th triglyceride percentile (Figure 4, bottom panel). However, adjusting the curves for BMI eliminates the significance of the regression slopes for all percentiles between the 5th and 95th triglyceride percentile, consistent with the adjusted regression slope.

An example where the classical model gives an incomplete result The classical model (Table 2) suggests that adjusting for regional adiposity has little effect on the relationship of men's BMI to triglycerides (i.e., adjusting for waist circumference changes the slope from 0.070 to 0.057 mmol/L per kg/m^2). Figure 4 (upper panel) is consistent with this conclusion; i.e. the adjusted curves largely coincide with the unadjusted curves, In fact, the ordinal relationship between the adjusted and unadjusted regression slopes of table 2 (waist adjusted<chest adjusted<unadjusted<hip adjusted) corresponds to the positions of the adjusted curves relative to the unadjusted curve in Figure 4. Different choices of waist, hip or chest circumferences produced similar curves for adjusted triglycerides versus adjusted BMI, therefore separate curves were not drawn for adjustment to small, intermediate, and large circumference.

However, the classical model presumes that a single slope describes the relationship of BMI to triglycerides. We have previously reported that the regression slope relating triglycerides to BMI depends upon the percentile of the triglyceride distribution (also shown in Figure 4 upper panel for reference). The new analyses presented in this report shows that this also is true when adjusted for body circumference measurements.

The false promise of indepencent effects A primary goal from multiple regression analyses of two independent variables (X and Z) on the dependent variable Y is to identify the independent effects of X on Y and Z on Y. This requires that the expected value of Y given X does not depend upon Z and correspondingly the expected value of Z given X does not depend upon Y. Although numerical solutions to these estimates can be produced by imposing the classical model onto the data, our analyses suggest that the solutions are likely to be wrong and conceptually misleading when relating plasma lipoproteins to adiposity. Under the classical model, the effect (slope) of X on Y adjusted for Z will never depend upon Z (Figure 2 upper panel) whereas the actual data suggests that the effect of adjusting triglycerides for BMI (Figure 2 bottom) very much depends upon the particular choice of BMI the data are adjusted to.

When applied to plasma HDL-cholesterol concentrations in relation to BMI and waist circumference, the classical model yields estimates for the independent effects for HDL-cholesterol versus BMI adjusted for waist circumference {-1.068 (0.070)} and for HDL-cholesterol versus waist circumference adjusted for BMI {-0.383 (0.099)}. The unadjusted curve of Figure 6 (upper panel) shows that the classical model does not apply for relating HDL-cholesterol to BMI (i.e., the regression slope becomes progressively more negative going from the 5th to the 95th HDL percentile). The effects of adjusting this relationship for waist circumference depends upon whether the data are adjusted to a small, intermediate or large (broader) waist circumference. The curves suggest that the BMI has a greater independent effect on HDL-cholesterol in the presence of a narrow waisted men than broad waisted men.

In conclusion, the classical regression model offers many conveniences to researchers. Yet the classical regression slope for men’s triglycerides versus waist circumference (2.349 mmol/L per m) applies only to a single percentile of the triglyceride distribution (60th percentile) while overestimating the slope for 59 percent of the distribution and over estimating the slope for 39 percent. Even the 95% confidence interval for the regression slope (2.065, 2.633) includes only a narrow range of the triglyceride distribution (i.e., the slopes falling between the (53rd and 65th percentiles). Under the classical model, an adjusted regression slope can be presented without reference to the particular selected value of the covariate (Figure 2, upper panel). However Figure 6, shows that the adjusted regression slope may depend upon both the percentile of the dependent variable and the percentile of the covariate. Our own experience from these and other data suggest that the cases where the classical model applies (e.g., Figure 6, bottom panel) represent the exception rather than the rule.

1. Despres JP, Prud'homme D, Pouliot MC, Tremblay A, Bouchard C. Estimation of deepabdominal adipose-tissue accumulation from simple anthropometric measurements in men. Am J Clin Nutr 1991; 54: 471-477.

2. Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indices of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994; 73: 460-468.

3. Ferland M, Despres JP, Tremblay A, Pinault S, Nadeau A, Moorjani S, Lupien PJ, Theriault G, Bouchard C. Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. Br J Nutr 1989; 61: 139-148

4. Lear SA, Chen MM, Frohlich JJ, Birmingham CL The relationship between waist circumference and metabolic risk factors: Cohorts of European and Chinese descent. Metabolism 2002;51:1427-32

5. Rheeder P, Stolk RP, Veenhouwer JF, Grobbee DE.The metabolic syndrome in black hypertensive women--waist circumference more strongly related than body mass index. S Afr Med J. 2002;92:637-41.

6. Halkes CJ, Castro Cabezas M, van Wijk JP, Erkelens DW.Gender differences in diurnal triglyceridemia in lean and overweight subjects. Int J Obes Relat Metab Disord. 2001;25:1767-74.

7. Hernandez-Ono A, Monter-Carreola G, Zamora-Gonzalez J, Cardoso-Saldana G, Posadas-Sanchez R, Torres-Tamayo M, Posadas-Romero C. Association of visceral fat with coronary risk factors in a population-based sample of postmenopausal women.Int J Obes Relat Metab Disord 2002;26:33-9

8. Van Pelt RE, Evans EM, Schechtman KB, Ehsani AA, Kohrt WM. Waist circumference vs body mass index for prediction of disease risk in postmenopausal women. Int J Obes Relat Metab Disord. 2001;25:1183-8.

9. Ohrvall M, Berglund L, Vessby B. Sagittal abdominal diameter compared with other anthropometric measurements in relation to cardiovascular risk. Int J Obes Relat Metab Disord 2000 24:497-501

10. Gustat J, Elkasabany A, Srinivasan S, Berenson GS. Relation of abdominal height to cardiovascular risk factors in young adults: the Bogalusa heart study. Am J Epidemiol 2000 1;151:885-91

11. Onat A, Sansoy V, Uysal O. Waist circumference and waist-to-hip ratio in Turkish adults: interrelation with other risk factors and association with cardiovascular disease. Int J Cardiol 1999 1;70:43-50

12. Caprio S, Hyman LD, McCarthy S, Lange R, Bronson M, Tamborlane WV. Fat distribution and cardiovascular risk factors in obese adolescent girls: importance of the intraabdominal fat depot. Am J Clin Nutr 1996;64:12-7

13. Williams PT. New paradigm for relating adiposity to low and high plasma triglyceride concentrations.

14. Williams PT. The relationships of vigorous exercise, alcohol and adiposity to low and high HDL-cholesterol levels

15. Efron B. The Jackknife, the bootstrap and other resampling plans. Society for Industrial and Applied Mathematics. 1982. Philadelphia, PA pp 1-92

16. Mosteller F, Tukey JW. Data analysis and regression. Addison-Wesley Publishing Co. Reading MA 1977, pp271--279.

17. Williams PT. Relationship of distance run per week to coronary heart disease risk factors in 8,283 male runners. The National Runners' Health Study. Arch Inter Med 1997, 157:191-198.

18. Williams PT. High density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners. N Engl J Med 1996; 334:1298-1303.

Table 1. Correlation between adiposity measurements								
	Men				Women			
		Circumferences				Circumferences		
	BMI	Waist	Hip	Chest		Waist	Hip	Chest
BMI	-	0.70	0.49	0.62	-	0.64	0.66	0.59
Waist circumference	0.70	-	0.61	0.57	0.64	-	0.60	0.59
Hip circumference	0.49	0.61	-	0.40	0.66	0.60	-	0.58
Chest circumference	0.62	0.57	0.40	-	0.59	0.59	0.58	-

All correlations significant at $P<0.0001$. Samples sizes for men were: BMI: 6,919; waist circumference: 6,763; hip circumference: 3,673; chest circumference: 5,946; and for women were: BMI: 2,312; waist circumference: 2,164; hip circumference: 2,109; chest circumference: 2,154.

Table 2. Standard regression slopes (SE) for the estimated effect of adiposity (independent variable) on plasma triglyceride and HDL-cholesterol concentrations (dependent variables)

	Body mass inde	Circumferences		
	(BMI, kg/m^2)	waist (m)	hip (m)	chest (m)
Men				
Triglycerides (mmol/L)				
unadjusted	0.070 (0.003)¶	2.349 (0.145)¶	0.968 (0.169)¶	1.520 (0.136)¶
BMI adjusted		0.719 (0.203)§	-0.269 (0.189	0.053 (0.171)
waist adjusted	0.057 (0.005)¶		-0.292 (0.210)	0.608 (0.165)§
hip adjusted	0.076 (0.006)¶	2.423 (0.240)¶		1.395 (0.191)¶
chest adjusted	0.069 (0.005)¶	1.904 (0.189)¶	0.456 (0.185)*	
HDL-cholesterol (mmol/L)				
unadjusted	-0.030 (0.002)¶	1.068 (0.070)¶	-0.494 (0.082)¶	-0.761 (0.065)¶
BMI adjusted		-0.383 (0.099)¶	0.020 (0.094)	-0.185 (0.083)*
waist adjusted	-0.024 (0.002)¶		0.120 (0.103)	-0.330 (0.079)¶
hip adjusted	-0.031 (0.003)¶	-1.160 (0.117)¶		-0.659 (0.093)¶
chest adjusted	-0.027 (0.002)¶	-0.881 (0.091)¶	-0.260 (0.090)†	
Women				
Triglycerides (mmol/L)				
unadjusted	0.031 (0.005)¶	1.045 (0.196)¶	0.337 (0.212)	0.829 (0.255)§
BMI adjusted		0.606 (0.254)*	-0.642 (0.280)*	0.023 (0.316)
waist adjusted	0.019 (0.007)†		-0.486 (0.263)	-0.021 (0.319)
hip adjusted	0.040 (0.007)¶	1.325 (0.252)¶		0.783 (0.323)*
chest adjusted	0.032 (0.007)¶	-1.098 (0.250)¶	-0.010 (0.262)	
HDL-cholesterol (mmol/L)				
unadjusted	-0.023 (0.003)¶	-1.051 (0.127)¶	-0.539 (0.138)¶	-1.234 (0.164)¶
BMI adjusted		-0.812 (0.165)¶	0.034 (0.184)	-0.902 (0.203)¶
waist	-0.010		0.127	-0.667

adjusted	(0.005)*		(0.171)	(0.204)§
hip adjusted	-0.023 (0.005)¶	-1.088 (0.162)¶		-1.165 (0.208)¶
chest adjusted	-0.013 (0.004)§	-0.745 (0.159)¶	-0.033 (0.169)	
Significance levels coded * p<0.05; † p<0.01; § p<0.001; ¶ p<0.0001				

Figure 1. Classical regression model of the dependent variable (Y) versus one independent variable (X). In the simple case where the relationship is described by a straight line, the data are distributed randomly about the line in accordance to a distribution that is the same for all X. In this case the regression slope at the 5th, 25th 85th or other percentiles will all be parallel.

Figure 2. Statistical adjustment by regression classical regression (upper panel), where each observation is projected to its expected value at X, for example. each plasma triglyceride concentrations is projected to its expected value at a BMI of 20 or 25 kg/m^2 using rays that pass through the point and are parallel to the calculated regression line (points adjusted to different values of BMI will differ by a constant), When the regression slopes are not parallel (differ depending upon the percentile of the triglyceride distribution), the relationship among adjusted values will defend upon the value of the covariate that the points are adjusted to.

Figure 3. Plot of the regression slopes of body mass index (BMI) versus waist, hip, and chest circumference for different percentiles of the BMI distribution.

Figure 4. Plot of the regression slopes of men's plasma triglyceride concentrations versus body mass index (BMI), and waist and hip circumferences. Curves are adjusted to an intermediate BMI of 23.5 (middle and bottom panels) and intermediate waist, hip, and chest circumferences of 0.82, 0.95, and 1.02 meters, respectively (upper panel).

Figure 5. Plot of the regression slopes of women's plasma triglyceride concentrations versus body mass index (BMI), and waist and hip circumferences. Curves are adjusted to intermediate waist circumference (0.69 m), intermediate chest circumference (0.86 m), and narrower (0.85 m) and intermediate (0.91 m) hip circumferences (upper panel); to narrower (0.85 m), intermediate (0.91 m), and broader (1.0 m) hip circumferences (middle panel); and to narrower (0.6 m), intermediate (0.69 m), and broader (0.77 m) waist circumferences (bottom panel).

Figure 6. Plot of the regression slopes of men's plasma high density lipoprotein (HDL) cholesterol concentrations versus body mass index (BMI), and waist and hip circumferences. Curves are adjusted to small (0.78 m), intermediate (0.82 m), and broader (0.92 m) waistlines (upper panel); leaner (20 kg/m^2), intermediate, (23.5 kg/m^2) and heavier (25 kg/m^2) BMIs (middle panel), and an intermediate BMI of 23.5 kg/m^2 (bottom panel).